REMARKS

Objections to the Specification

Previously pages 12 and 15 were amended to add pertinent sequence identifiers and then these pages were amended a second time wherein the sequence identifiers were inadvertently omitted. Pages 12 and 15 have been amended again herein to reintroduce the pertinent sequence identifiers. No new matter has been added.

Rejection of Claims Under 35 U.S.C. §103(a)

Claims 1, 10 and 19, and claims dependent thereon, are rejected under 35 U.S.C. §103(a) as being unpatentable over Koike et al. in view of Miraglia et al. Specifically the Office Action states that the burden of establishing whether or not the prior art oligonucleotide and SN-38 prodrug has the further function of "statistically significantly potentiating the activity of the prodrug" under generally any assay conditions falls to the Applicant.

Applicant respectfully disagrees. Before any burden falls to the Applicant, the Office Action must first establish that there is a motivation to combine the cited references. Such a motivation to combine clearly lacks in this case. Applicant reiterates that Koike does not describe the coadministration of an oligonucleotide and a SN-38 prodrug. Rather, Koike describes cells transfected with an expression vector having an 805bp transcript complementary to cMOAT that is synthesized *in situ* followed by the administration of CPT-11 to these cells.

Miraglia fails to provide the teachings Koike lacks. In contrast to Koike, Miraglia describes antisense oligonucleotides. However, Miraglia is silent with regards to the coadministration of an antisense oligonucleotide and a SN-38 prodrug; how such a coadminstration could be achieved; and whether there would be a synergistic effect realized by such a coadministration.

Moreover, Miraglia describes antisense oligonucleotides to mdm-2. MDM-2 is an ubiquitin ligase for p53 (and itself) and plays a role in targeting a protein for degredation. Whereas Koike discusses cMOAT, which is a transmembrane protein located in liver cells. Although cMOAT (canicular multi-organic anion transporter) is a member of the multidrug resistance proteins, cMOAT is a cell membrane anion transporter protein, which plays a substantially different role in multidrug resistance than does MDM-2, an ubiquitin ligase. . Thus,

one skilled in the art would not have any reason to believe, based upon Koike, that coadministration of an antisense for a ubiquitin ligase with irrinotecan would be successful.

During the exhaustive prosecution history of the instant application, Koike has been cited in several previous 35 U.S.C. §102 and §103 rejections, each of which have been overcome. The instant rejection is essentially identical to the previous §103 rejection over Koike in view of Baracchini except that Koike is now combined with Miraglia.. In principle, there is no difference between the Baracchini and the Miraglia references. At most, both references describe antisense oligonucleotides. This fact alone, however, is not enough to replace the substantial deficiencies of Koike. It appears that the Office Action is examining the claims in a "problem-solution approach". However, this route for the assessment of inventiveness has inherent drawbacks, e.g., the danger of the application of **hindsight**.

To avoid looking at the prior art with the benefit of teachings of the instant application, a proper determination of the inventiveness of the presently claimed invention would be to investigate the question whether Koike and Miraglia contain any particular pointer in the direction of the claimed invention, i.e., to motivate an expert having average knowledge and experience and not knowing the present invention to provide the instantly claimed methods.

As discussed above, there is no suggestion or motivation to combine Koike and Miraglia for any purpose, much less in order to render the instant invention obvious. Reconsideration and withdrawal of the instant rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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